REMARKS

Claims 56, 69-76 and 78 are pending. Applicants thank the Examiner for withdrawing objection to the claim 78 and the information disclosure statement.

Claim Rejections – 35 USC § 103

Claims 56, 70-76 and 78 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Sampath et al. ("Sampath") in view of London et al. ("London"). The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the pharmaceutical containing an OP/BMP morphogen, as allegedly taught by Sampath, by formulating a pharmaceutical further encompassing an ACE inhibitor, as allegedly taught by London.

Further, claims 56 and 69 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Sampath in view of London as applied to claims 56, 70-76 and 78 in the preceding paragraphs and further in view of Salvetti ("Salvetti"). The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate a pharmaceutical comprising an OP/BMP morphogen, as allegedly referred to by Salvetti, and further comprising an ACE inhibitor, as allegedly referred to by London, said ACE inhibitor being enalapril, as allegedly referred to by Salvetti. The Examiner also alleges that synergy is not per se a proof of unexpected result because, allegedly, sometimes synergy can be expected.

Applicants respectfully disagree with the Examiner's characterization of what one of ordinary skill in the art would have done. In 2000, the inventors and their colleagues published a paper which included the comparison of the effect of bone morphogenetic protein -7 (BMP-7, a.k.a.

OP-1) and angiotensin-converting enzyme (ACE) inhibitors on renal dysfunction models. Hruska et al. Am. J. Physiol. Renal Physiol. 280: F130–F143, 2000. In this article the authors explain the proposed mechanism of action of OP-1 and ACE inhibitors as agents to treat renal dysfunction. In their experimental model, the dysfunction is successfully treated with either ACE or OP-1. The publication explains how these agents are understood to have effect on the damage cascade.

> An early event in the damage cascade is angiotensin II upregulation, which stimulates tumor necrosis factor-a (TNF-a) production and TGF-b expression. These cytokines activate nuclear factor kB (NF-kB) (22, 34), a crucial transcription factor in fibroblasts, macrophages, and epithelial cells, leading to expression of a-SMA, type IV collagen, osteopontin, MCP-1, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1, in addition to other genes (44), involved in renal cellular transformation and apoptosis as well as interstitial inflammation and subsequent fibrosis. . . . [W]e and others have demonstrated that ACE inhibition, type 1 angiotensin II receptor blockade, or reduction of angiotensin gene expression is protective against the activation of the damage cascade and against interstitial fibrosis.
>
> * * *
>
> The effects of ACE inhibition are mediated, in part, through inhibition of intrarenal paracrine functions of angiotensin II, which activates a damage cascade of cytokines and transcription factors in response to renal injury. OP-1 also inhibited the activation of the damage cascade as part of its mechanism of renal protection.
>
> * * *
>
> ACE inhibition decreases the activity of the damage cascade by suppressing UUO stimulation of TGF-b, TNF-a, and NF-kB, which are mediated by angiotensin II. [citation omitted]

It would be more likely and expected for two drugs to work in at least additive and possibly synergistic manner if each works on a different target. It would be less likely for two drugs that work on the same target to exhibit additive or synergistic effect. In fact, it would be expected that the effect would be less than additive, as two drugs may interfere with each other or would overlaps

and be redundant compared to when used alone. In the present case, although mechanism of action by OP-1 is not well understood, the protective effect of the two agents stems in part from protection of the renal tissue from the same damage cascade. Therefore, Applicants submit that it was unexpected that enalapril and OP-1 would have synergistic effect.

Further, Applicants respectfully submit that enalapril as an example of the broad class of compounds that are all ACE inhibitors is appropriate for the scope of the claim reciting ACE inhibitors. As quoted in Hruska et al. above, ACE inhibitors are effective in renal protection because elevated levels of angiotensin II is part of the damage cascade. No matter what the mechanism, as long as a compound is an ACE inhibitor, angiotensin II is reduced and the damage cascade is alleviated. Therefore, it is appropriate to use one compound as representing a whole class of inhibitors which class is defined by a function.

Applicants have disclosed unexpectedly superior properties in the claimed compositions over a spectrum of properties. The combination of the OP/BMP morphogen and the ACE inhibitor exhibit at least two unexpected advantageous properties: superior treatment of proteinuria and superior increase in GFR as compared to the morphogen alone or the ACE inhibitor alone. These unexpected properties of the claimed combination are sufficient to rebut a *prima facie* case of obviousness.

Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Obviousness-Type Double Patenting

Claims 56, 71-76 and 78 remain rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being obvious over claims 1-13 of U.S. Patent No. 6,677,432 ('432) *or* claims 1-5 of U.S. Patent No. 6,846,906 ('906) for the reasons alleged by the Examiner in the previous office action.

Further, claims 56 and 69 stand rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being obvious over claims 1-13 of U.S. Patent No. 6,677,432 ('432) *or* claims 1-5 of U.S. Patent No. 6,846,906 ('906) in view of London as applied to claims 56, 71-76 and 78 in the preceding paragraphs and further in view of Vukicevic and Salvetti. for the reasons alleged by the Examiner in the previous office action.

In response, Applicants will consider filing a suitable disclaimer upon notification of allowable subject matter.

The Office Action provisionally rejects claims 56, 69, 71-76 and 78, under the judicially created doctrine of obviousness-type double patenting as being unpatentable over co-pending Application No. 10/816,768. In response, Applicants submit that, pursuant to MPEP 804, "[i]f the 'provisional' double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the 'provisional' double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent." Therefore, Applicants are not required to amend the claims at this time.

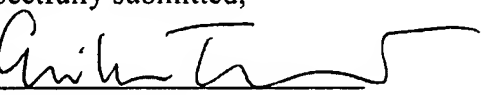
CONCLUSIONS

In view of the above amendments, Applicants believe the pending application is in condition for allowance.

Applicants believe no additional fee is due with this response beyond those listed in the fee transmittal sheet. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. JJJ-P01-599 from which the undersigned is authorized to draw.

Dated: October 10, 2007

Respectfully submitted,

By 

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